COMMENTARY

Unnecessary Use of Placebo Controls

The Case of Asthma Clinical Trials

THE ETHICS of placebo-controlled clinical trials has generated considerable controversy in recent years. Critics, often citing the Declaration of Helsinki, have argued that use of placebo controls is unethical in trials of medications to treat conditions for which proven effective treatments exist. Defenders of placebo-controlled trials contend that the alternative of clinical trials that compare active treatments without placebo controls are often subject to serious methodological weaknesses. In the present article we develop a middle-ground position on the ethics of placebo-controlled trials, which is applied to recent clinical trials of treatments for asthma. Questions are raised about 3 recent placebo-controlled asthma trials on the grounds that the scientific questions that these trials were designed to answer did not require use of placebo. However, use of placebo controls in initial trials of investigational treatments is defended, provided that patient volunteers randomized to placebo are not exposed to serious risks of irreversible harm or intolerable discomfort.

BACKGROUND

The randomized, double-blind, placebo-controlled clinical trial is widely regarded as the gold standard for testing treatment efficacy. The use of placebo provides a methodological control to account for improvement in study subjects that is not related to the specific treatments under investigation.[1] Despite strong methodological reasons for the use of placebo controls, ethical controversy surrounds placebo-controlled trials, especially when patient volunteers randomized to placebo have effective treatments withdrawn or withheld during the course of the clinical trial. Recently, debate about the ethics of placebo controls has intensified in the medical literature.[2-5]

In the present article we develop a position on the ethics of placebo-controlled trials, which we use to critically examine 3 recent placebo-controlled asthma clinical trials. We argue that placebo controls were unnecessary to answer pertinent scientific and clinical questions in these trials—one focusing on the addition of a leukotriene antagonist to an inhaled corticosteroid in patients needing additional controller therapy,[6] one testing a combination of 2 proven effective therapies in a novel delivery device,[7] and one comparing single vs twice-daily administration of an equivalent total dose of an inhaled corticosteroid.[8] Subjects randomized to placebo in these clinical trials were exposed to risks of harm or discomfort without compensating benefits in terms of knowledge to be gained by the research. In contrast, placebo controls are justifiable in initial trials of investigational treatments, such as the leukotriene antagonists,[9,10] to provide definitive demonstration of efficacy and to avoid exposing large numbers of subjects to potentially ineffective or toxic treatments. Recommendations are offered for limiting the number of subjects exposed to placebo in such initial efficacy trials and developing historical databases of placebo-controlled results to be used, where needed, in validating active-controlled equivalence trials.

THE ETHICAL DEBATE

Opponents of placebo-controlled trials in conditions for which proven effective treatments exist criticize the use of placebo controls as unethical because they deny patients medically indicated therapy or investigational treatment that shows promise of being at least as effective as standard therapy.[2,11,12] Consequently, patients seeking treatment in these clinical trials who are randomized to placebo receive care known to be inferior to standard therapy. These commentators have supported their position by citing the World Medical Association's Declaration of Helsinki. Revised in October 2000, the Declaration of Helsinki now contains a more clearly formulated provision governing the ethics of placebo-controlled trials:

> The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.[13]

Critics of placebo-controlled trials also contend that when proven effective treatments exist, there is no scientific or clinical value in testing whether a novel treatment is better than an inert placebo. It should be compared instead with a standard treatment.[11,12]

Defenders of placebo-controlled trials argue that such a cat-

egorical prohibition of the use of placebo controls is unreasonable.[3-5] It would rule out the use of placebo in valuable clinical trials that pose little or no risks of serious harm to human subjects. In addition, they contend that the alternative of active-controlled trials, designed to test for the equivalence or "noninferiority" of investigational and standard treatments, are subject to methodological weaknesses. Trial results indicating absence of significant difference between the investigational and standard treatment do not imply that the investigational treatment is effective. These active-controlled equivalence trials lack "internal validity," that is, the efficacy of the investigational agent must be validated by reference to well-controlled data external to the clinical trial. This methodological critique does not impugn active-controlled trials designed to test whether experimental treatments are superior to standard therapy.[4] Without placebo-controlled studies, novel treatments that are no more effective than placebo might gain approval because the only available data come from trials designed as active-controlled equivalence investigations. In addition, proponents of placebo-controlled trials argue that they are more efficient insofar as they typically require smaller sample sizes to achieve valid results.

The debate has been characterized as one of "science vs ethics."[14] But this is a false dichotomy. Scientific validity is a basic requirement of the ethics of clinical research.[15] No human subjects should be exposed to risks in methodologically flawed studies that lack the power or rigor to produce interpretable results. Although the debate has become polarized, both sides articulate ethically relevant considerations, suggesting that a middle-ground position may have merit.

TYPOLOGY OF PLACEBO-CONTROLLED TRIALS

In general, placebo-controlled trials do not pose ethical problems when no treatments exist for a disorder or standard treatments have never been proven effective. Ethical concern focuses on those conditions with proven effective treatments. In the latter case, placebo-controlled trials can be classified into 3 categories for the purpose of ethical analysis. First are trials in which patients randomized to placebo are exposed to substantial risks of death, irreversible harm, or intolerable discomfort. Examples include trials of investigational chemotherapeutic agents for potentially fatal cancers and novel antibiotics for life-threatening infectious diseases. There is a consensus that in such cases placebo controls that involve withholding effective treatment are unethical. However, in these situations placebos are justifiable in testing investigational add-on or combination treatment, provided that all patient volunteers receive standard, proven effective therapy.

A second category focuses on studies in conditions for which withholding treatment during short-term clinical trials poses no risk of serious harm and is not likely to result in anything more than mild to moderate discomfort. These include placebo-controlled trials for conditions such as headaches, heartburn, and allergic rhinitis, in which symptoms are not severe. Moreover, high rates of placebo response in these conditions make the use of placebos methodologically necessary for valid clinical trials. Because individuals with these illnesses often knowingly elect to forgo medication without risking impairment of their health, their informed consent to be randomized to an investigational treatment or placebo is sufficient to justify the use of placebo controls.[5] Interpreted literally, the Declaration of Helsinki prohibits this class of placebo-controlled trials; however, it is difficult to see what serious ethical objection may be lodged against the use of placebo in these cases. Though commentators may differ over whether the risk of harm or severe discomfort is "trivial" with respect to particular conditions, most concur that these types of trial are ethically acceptable.

A third category of clinical trials encompasses a wide range of diseases in which withholding treatment poses greater risk of harm and more severe discomfort but where these risks can be minimized in carefully designed and monitored short-term studies. This category consists mostly of trials in chronic conditions for which current treatments are symptomatic or prophylactic without being curative. Asthma falls into this category, along with stable angina, migraine headaches, and depression. Owing to the potential for harmful consequences, placebo controls require a sound methodological rationale. Once again, informed opinion may differ about whether trials of treatments for specific conditions belong in this category.

PLACEBO-CONTROLLED TRIALS IN ASTHMA

Inhaled corticosteroids are the cornerstone of asthma therapy. The National Heart, Lung, and Blood Institute guidelines recommend them for all patients except those with mild intermittent asthma.[16] Newer options for treating asthma include long-acting β-agonists and antileukotriene agents, as well as combinations of these newer alternatives with inhaled corticosteroids.

The ethical justifiability of placebo controls in clinical trials depends critically on the patient population under investigation, the known efficacy of current treatments, and the scientific and clinical questions that the studies are designed to answer. Three recent asthma clinical trials, outlined in the **Table**, offer an instructive case study in the ethics of placebo controls.[6-8] The first 2 compared different combinations of therapies with corticosteroid monotherapy and placebo, and the third evaluated twice-daily vs single-daily administration of an equivalent dose of the same inhaled corticosteroid compared with placebo.

In all 3 studies, patients randomized to placebo fared significantly worse with respect to primary and secondary outcome measures: forced expiratory volume in 1 second (FEV_1) at the end of the study compared with baseline, asthma symptom scores, withdrawal owing to asthma exacerbations, and use of albuterol.[6-8] These results do not suggest that the subjects receiving placebo were irreversibly harmed; however, they were placed at some risk of harm from asthma exacerbation and experienced symptoms associated with discomfort, which may have caused temporary functional disability. Without

Study Characteristics

Study	Subjects	Total Sample Size	Age Range, y	Mean FEV_1* at Study Entry, % Predicted	Study Arms	Trial Duration, wk
Laviolette et al[6] (study 1)	History of at least 1 y of intermittent or persistent asthma	642	15-78	72	(1) Beclomethasone dipropionate + montelukast sodium (n = 193) (2) Beclomethasone dipropionate (n = 200) (3) Montelukast sodium (n = 201) (4) Placebo (n = 48)	16
Kavuru et al[7] (study 2)	History of asthma for at least 6 mo requiring therapy	354	12-70	64	(1) Fluticasone propionate + salmeterol (n = 92) (2) Fluticasone propionate (n = 92) (3) Salmeterol (n = 90) (4) Placebo (n = 82)	12
ZuWallack et al[8] (study 3)	History of chronic asthma requiring therapy for 6 mo prior to enrollment	253	12-69	67	(1) Fluticasone propionate, 250 µg twice daily (n = 86) (2) Fluticasone propionate, 500 µg once daily (n = 83) (3) Placebo (n = 84)	12

*FEV_1 indicates forced expiratory volume in 1 second.

a solid methodological rationale for placebo, it is difficult to justify exposing patient volunteers to the risks and discomforts of withholding or withdrawing effective treatment.

Trials of Combination Therapy

Characteristics of the 2 placebo-controlled combination therapy trials are detailed in the Table.[6,7] Both studies included placebo controls despite the fact that they were powered to detect significant differences between the active combination and monotherapies. The statistical analysis section of the first study stated:

> This sample size allowed detection, with 95% power (at $\alpha = 0.05$; two-sided test), of a 6.0 percentage point difference in FEV_1 (percent change from baseline) and a 10.0% difference in daytime symptoms score (change from baseline) between the additivity and beclomethasone treatment groups.[6]

The power analysis for the second study similarly made no mention of the subjects treated with placebo in the determination of sample size required to test the study's hypotheses.

In each of these trials there was no clear and compelling scientific or clinical rationale for placebo controls. Either protocol could have been designed as an active-controlled superiority trial, producing 2 advantages. First, an active-controlled superiority trial would have avoided exposing asthmatic patients in need of maintenance treatment to placebo for up to 12 or 16 weeks. Second, without the unnecessary use of placebo, these trials would have required fewer subjects, making them more efficient and less costly.

In the first study, the authors stated, "The placebo group was included to validate the clinical benefit from inhaled corticosteroid treatment."[6] However, demonstrating the superiority of the combination therapy to monotherapy would logically provide all the validation needed for this clinical trial. Moreover, because all the active treatments were approved medications that had been shown to be superior to placebo in previous clinical trials,[17-19] comparison with placebo did not add valuable scientific information.

Demonstrating that the combination therapies were superior to placebo also lacks clinical value. Combination therapy should be administered in clinical practice only if it is likely to be more effective than monotherapy. In fact, both studies showed that combination therapy was superior to monotherapy—outcomes that could be demonstrated without comparison with placebo.

We can only speculate why placebo controls were thought to be needed in these 2 studies. One reason might be the belief that the Food and Drug Administration (FDA) requires placebo controls for asthma clinical trials. This is suggested by the fact that the first study, which enrolled patients in 18 countries, included placebo controls only in US sites. (The second study was conducted exclusively in the United States.) Although FDA guidelines appear to favor placebo controls whenever studies do not pose risks of serious, irreversible harm, they do not question the credibility of active-controlled superiority trials, in contrast to active-controlled equivalence trials.[4,20] Hence, use of placebo in the first 2 examples, which could have been executed as active-controlled superiority trials, would not find any justification in this appeal to FDA requirements. Furthermore, the FDA is not an authoritative arbiter of the ethics of clinical trials. Institutional review boards have the authority to make independent judgments of the ethical justifiability of placebo controls.

Comparison of 2 Dosing Regimens

Methodological objections to use of placebo controls are more nuanced in the third example in our illustrative case study comparing once- or twice-daily administration of the same total daily dose of fluticasone propionate (Table).[8] Previous clinical trials had demonstrated the efficacy of twice-daily dosing of this inhaled corticosteroid. Comparison between once- and twice-daily dosing could provide clinically useful information in view of the greater potential convenience and pros-

pect of enhanced compliance from once-daily administration. In theory, an adequately powered active-controlled equivalence trial of these 2 dosing regimens might be subject to the methodological challenge that noninferiority of once-daily administration would not necessarily imply efficacy. Yet the historical results of recent placebo-controlled trials with similar entry criteria, duration, and outcome measures might have been used to validate efficacy by comparing those who previously received placebo with the outcome of patients randomized to either of the 2 dosing regimens of fluticasone propionate. As it turned out, patients in the twice-daily group fared better on some of the outcome measures.

Can Informed Consent Justify Placebo Controls?

It might be objected that informed consent provides adequate justification for placebo controls in these asthma clinical trials. This is mistaken because risk-benefit assessment constitutes an independent ethical requirement of clinical research.[15] Prospective subjects should not be invited to enroll in research unless institutional review boards have previously determined that the risks of the research are justified by the anticipated benefits to the subjects or by the potential benefits of the knowledge to be gained. These 3 studies did not require the use of placebo controls to achieve their scientific aims; accordingly, there were no potential scientific, or therapeutic, benefits to justify the risks for patient volunteers randomized to placebo.

Initial Trials of Investigational Agents

A more complex ethical analysis is needed to evaluate the use of placebo controls for initial trials of investigational treatments, which include experimental drugs and approved drugs that have not been validated for a particular indication. Placebo controls also expose patient volunteers in such trials to risks from withholding effective treatment. However, definitive demonstration of efficacy should be required to approve or validate new treatments. Initial short-term placebo-controlled trials offer an efficient way to establish efficacy. Active-controlled equivalence trials typically require larger sample sizes[21] and remain subject to methodological challenge. Before being evaluated in considerably larger-scale active-controlled trials, testing equivalence, or superiority, investigational agents should pass the test of efficacy in initial placebo-controlled trials.

Smaller-scale but adequately powered placebo-controlled trials minimize the number of subjects required to reject inferior investigational treatments. This is not a matter solely of efficiency. Potentially promising experimental treatments may turn out to be ineffective or produce unacceptable adverse effects. The risks of withholding treatment for relatively small numbers of subjects during initial placebo-controlled trials need to be balanced against the risks of exposing many more subjects to potentially ineffective or toxic treatments in active-controlled trials.[22] The number and scale of placebo-controlled trials requisite to demonstrate initial efficacy is a matter of debatable judgment. A series of well-designed, comparable placebo-controlled trials that do not enroll more subjects than needed to establish initial efficacy provides the foundation for a historical database that can be used to validate subsequent active-controlled trials.[23-25] Historical clinical trial data, however, must be used with caution, owing to changes over time in the characteristics of patients, standard treatments, and other factors that may affect comparability with contemporary trial data.

CONCLUSIONS

The placebo control is a powerful methodological tool, which can promote rigor and efficiency in clinical trials. However, placebo controls that involve withholding effective treatment pose risks of harm and discomfort to trial participants. Accordingly, they should be used sparingly, mainly in initial trials to test the efficacy of investigational agents. In protocols submitted to institutional review boards and manuscripts submitted to scientific journals, investigators should be required to provide compelling justifications for use of placebo controls in clinical trials. The ethics of clinical research depends on the cooperation and diligence of investigators, institutional review board members, and journal editors. Finally, consideration should be given to developing historical control databases drawn from well-designed placebo-controlled trials for use in validating the results of active-controlled trials.

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